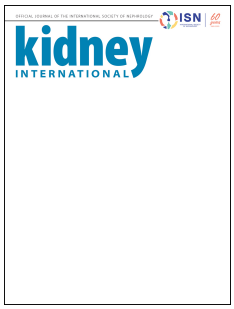
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Pre-exposure prophylaxis with 300 mg Evusheld™ elicits limited neutralizing activity against the Omicron variant

Ilies Benotmane, MD, Aurélie Velay, PharmD PhD, Gabriela Gautier Vargas, MD, Jérôme Olagne, MD, Olivier Thaunat, MD PhD, Samira Fafi-Kremer, PharmD PhD, Sophie Caillard, MD PhD

PII: S0085-2538(22)00383-0

DOI: https://doi.org/10.1016/j.kint.2022.05.008

Reference: KINT 3061

To appear in: *Kidney International*

Received Date: 29 April 2022

Accepted Date: 13 May 2022

Please cite this article as: Benotmane I, Velay A, Vargas GG, Olagne J, Thaunat O, Fafi-Kremer S, Caillard S, Pre-exposure prophylaxis with 300 mg Evusheld™ elicits limited neutralizing activity against the Omicron variant, *Kidney International* (2022), doi: https://doi.org/10.1016/j.kint.2022.05.008.

Pre-exposure prophylaxis with 300 mg Evusheld™ elicits limited neutralizing activity against the Omicron variant

Ilies Benotmane, MD[1], Aurélie Velay, PharmD PhD[2], Gabriela Gautier Vargas, MD[1], Jérôme Olagne, MD[1], Olivier Thaunat, MD PhD[2], Samira Fafi-Kremer, PharmD PhD[3], Sophie Caillard, MD PhD[1]

[1] Department of Nephrology and Transplantation, Strasbourg University Hospital, 67000 Strasbourg, France

[2] Hospices Civils de Lyon, Edouard Herriot Hospital, Department of Transplantation, Nephrology and Clinical Immunology, 5, place d'Arsonval, 69003 Lyon, France

[3] Department of Virology, Strasbourg University Hospital, 67000 Strasbourg, France

Corresponding author: Sophie Caillard, Department of Nephrology, Dialysis and Transplantation, Strasbourg University Hospital, 1 place de l'hôpital, 67091 Strasbourg, France

Email: Sophie.caillard@chru-strasbourg.fr; phone: 0033369551320

Keywords: kidney transplant recipients, SARS-CoV-2, omicron variant, tixagevimab, cilgavimab, neutralizing activity

Immunocompromised patients show an impaired vaccine-induced immune response, resulting in an increased risk of severe Covid-19 (1). In an effort to address this issue, health authorities in the US and various European countries have subsequently authorized the use of anti-SARS-CoV-2 monoclonal antibodies for pre-exposure prophylaxis. While the combination of casirivimab–imdevimab (Ronapreve™, Roche Regeneron) has been shown to confer satisfactory protection against the delta variant, it has limited neutralizing activity against omicron (3). In March 2022, the combination of cilgavimab–tixagevimab (Evusheld™, Astra Zeneca) has been approved in the UK for protecting transplant recipients with poor response to vaccination against the omicron variant (3). In France, Evusheld™ has also been granted approval as of December 2021. While the PROVENT study (Phase III Double-blind, Placebo-controlled Study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adult) showed a good efficacy of 300 mg Evusheld™ in the context of delta variant circulation, the question as to whether this dosage may be sufficient to prevent the omicron infection remains unanswered. Previous data indicated that the serum neutralizing capacity against SARS-CoV-2 is positively associated with protection against severe forms of Covid-19 (4). Here, we analyzed the neutralizing capacity against omicron in a cohort of kidney transplant recipients who received Evusheld™ for pre-exposure prophylaxis.

Both anti-RBD IgG titers and neutralizing antibody titers against the omicron BA.1 variant were measured in serum samples collected from 63 adult kidney transplant recipients who received gluteal intramuscular prophylactic injections of Evusheld™ (150 mg tixagevimab and 150 mg cilgavimab) in the Lyon and Strasbourg University Hospitals. Recipients with a history of Covid-19 or positive anti-nucleocapsid IgG were excluded. Patients who received prophylactic Ronapreve™ (600 mg casirivimab and 600 mg imdevimab, n = 39) and those who were infected with SARS-CoV-2 during the fifth wave of the pandemic (n = 14) were used as the negative and positive control groups, respectively. The study protocol was

approved by the local Ethics Committees (identifier: DC-2013–1990 and DC-2021-4460) and written informed consent was obtained from all participants.

After a median interval from injection of 29 days [IQR 29-33], patients who received Evusheld™ had a low neutralizing activity (Figure 1A) and only 9.5% of them (6/63) were able to neutralize the omicron variant compared to 71% of patients [10/14] who were infected with SARS-CoV-2 and 2.6% [1/39] of those who received Ronapreve™. Interestingly, convalescent patients displayed higher levels of neutralizing antibodies than those who received Evusheld™ (median: 2.3 log IC50, interquartile range [IQR]: 1.5−2.7 *versus* 0.00 log IC50, IQR: 0−0.05; p<0.001). While anti-RBD IgG titers were generally low after Evusheld™ injection (median: 2583 binding antibody unit (BAU)/mL, IQR: 1906−3611 BAU/mL), a high interindividual variability was observed (range: 262−7032 BAU/mL, figure 1B). This variability was largely explained by the patients' body mass index, which showed an inverse correlation with anti-RBD IgG titers (Figure 1c). Further analysis revealed that participants with anti-RBD titers <2500 BAU/mL after Evusheld™ injection had no neutralizing activity (Figure 2). Furthermore, seven patients of this cohort developed symptomatic Covid-19 including two who required hospitalization. All had negative neutralizing activity at the time of infection diagnosis.

Taken together, these data indicate that less than 10% of patients who received Evusheld™ were able to neutralize the omicron BA.1 variant at 29 post-injection days. Therefore, the dose of 300 mg Evusheld™ is likely insufficient to achieve the required neutralization activity *in vivo*. These findings corroborate those of a recent study conducted in transplant recipients who received three vaccine doses (5); specifically, the authors reported that anti-RBD levels associated with serum neutralizing activity against omicron in this population were approximately 8500 BAU/mL (5). Finally, our study also supports recent FDA recommendations (6), derived from *in vitro* models, regarding the need to increase the dose of

Evusheld™. To our knowledge, data on the effectiveness of tixagevimab−cilgavimab in the prevention of omicron BA.2 infection have not yet been published. Research aimed at assessing the correlation between anti-RBD titers after Evusheld™ administration and the *in vivo* neutralizing capacity against the BA.2 omicron variant is currently ongoing.

Conflict of Interest Disclosures

Sophie Caillard and Olivier Thaunat received consultant fees from Astra Zeneca. All other authors declare that they have no conflicts of interest.

References

1. Caillard S, Thaunat O. COVID-19 vaccination in kidney transplant recipients. Nat Rev Nephrol. 2021 Dec;17(12):785-787.
2. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature. 2022;602(7898):671-675.
3. https://www.gov.uk/government/publications/regulatory-approval-of-evusheld-tixagevimabcilgavimab (Published 17 March 2022)
4. Charmetant X, Espi M, Benotmane I, et al. Infection or a third dose of mRNA vaccine elicit neutralizing antibody responses against SARS-CoV-2 in kidney transplant recipients. Sci Transl Med. 2022 Feb 1:eabl6141. doi: 10.1126/scitranslmed.abl6141. Epub ahead of print. PMID: 35103481.
5. Kumar D, Hu Q, Samson R, Ferreira VH, et al. Neutralization against Omicron variant in transplant recipients after three-doses of mRNA vaccine. Am J Transplant. 2022 Mar 10. doi: 10.1111/ajt.17020. Epub ahead of print. PMID: 35266606.
6. https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-evusheld-dosing. Last access 24 Feb 2022

Figure legends

Figure 1A

Serum neutralizing IgG titers (log IC50) measured with a previously described in-house viral pseudoparticle-based assay (4) in three groups of kidney transplant recipients. Circles denote titers measured at 28 post-injection days in patients (n = 63) who received Evusheld™ (300 mg), whereas triangles indicate titers quantified at 31 post-injection days in patients (n = 39) who received Ronapreve™ (1200 mg). Squares denote titers measured at 27 post-infection days in patients (n = 14) who were infected with SARS-CoV-2. Dotted line represents the neutralizing positivity threshold (1.6 log IC50). Groups were compared with the Kruskal-Wallis test. The contingency graphs at the bottom of the figure indicate the percentages of patients with neutralizing activity in each group with (positive in black and negative in gray; the percentage is reported in the middle).

Figure 1B

Anti-RBD IgG titers (BAU/mL, Abbott Architect, Chicago IL, USA) 28 days after Evusheld™ injection (300 mg) in 27 patients who did not receive Ronapreve™ before Evusheld™.

Figure 1C

Correlation between body mass index (kg/m^2) and anti-RBD IgG titers (BAU/mL, Abbott Architect, Chicago, IL, USA) 28 days after Evusheld™ injection (300 mg) in 27 patients who did not receive Ronapreve™ before Evusheld™; $r^2=0.595$.

Figure 2

Correlation between anti-RBD IgG (Abbott Architect, Chicago, IL, USA) and neutralizing antibody titers (3) in three groups of kidney transplant recipients. Circles denote titers measured at 28 post-injection days in patients (n = 63) who received Evusheld™ (300 mg), whereas triangles indicate titers quantified at 31 post-injection days in patients (n = 39) who received Ronapreve™ (300 mg). Squares denote titers measured at 27 post-infection days in patients (n = 14) who were infected with SARS-CoV-2.

Figure 1A

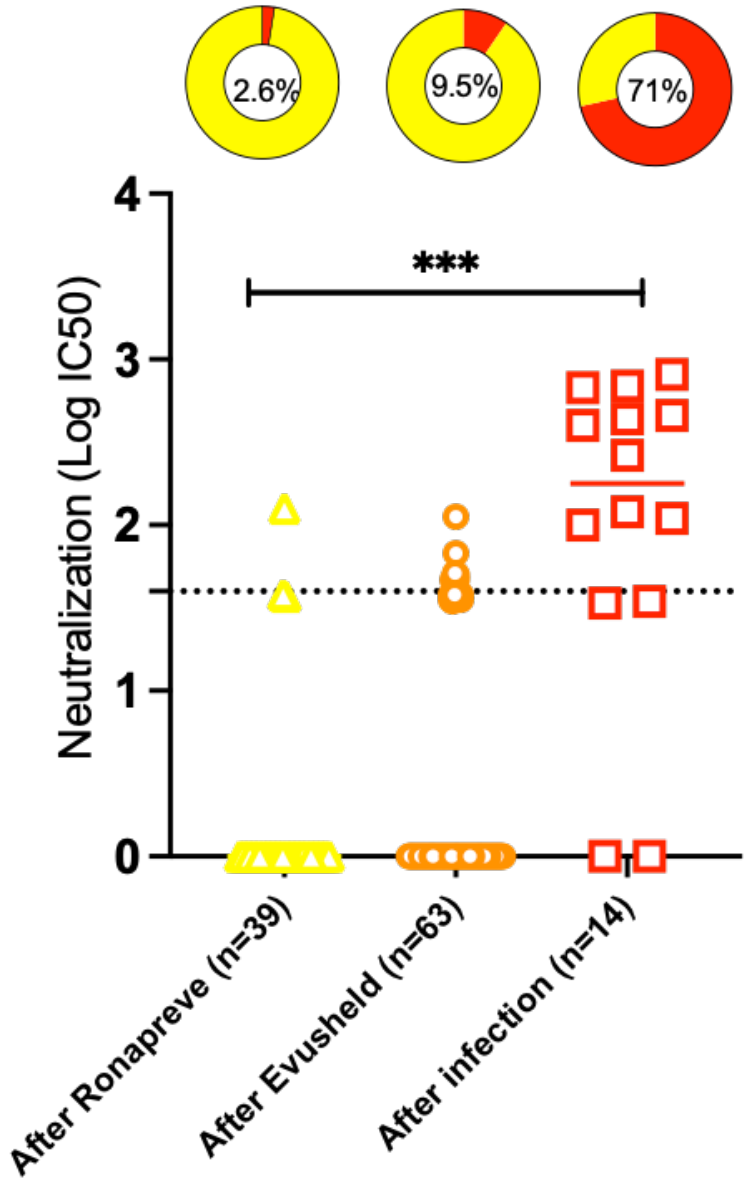


Figure 1B

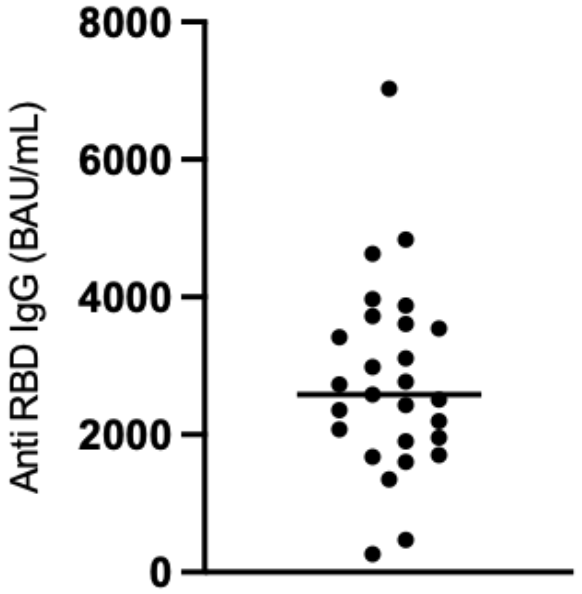


Figure 1C

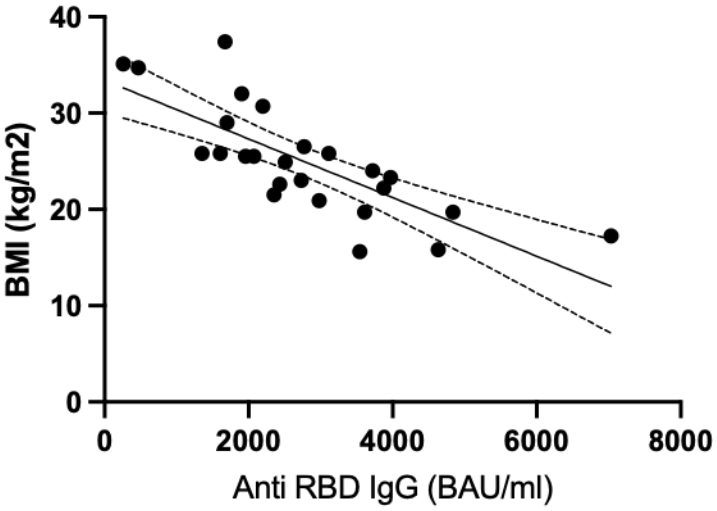


Figure 2